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Intralesionally Implanted Cisplatin Cures Primary Brain Tumor in Rats

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Background and Objectives: Chemotherapy has added little to the overall survival of the patients with primary malignant brain tumors, primarily due to its difficulty penetrating the blood-brain barrier. Use of polymers, releasing high doses of chemotherapy locally over time, is a promising new treatment strategy. Three experiments were conducted to test the effect of cisplatin, released from biodegradable polymer, on rats with 1 week established brain tumor.

Methods: 9L gliosarcoma cells and drug-free or cisplatin-loaded polymer were administered through a right frontal lobe cannula in male Fischer 344 rats. Tumor cells were infused on day 0 and polymer on day 7. Animals were monitored for 60 days.

Results: In experiment one, 0.5 mg/m^2 of cisplatin loaded in polymer resulted in a mean survival time (MST) of 51 ± 14 days with 63% (10/16) rats surviving to day 60. MST for the control group was 24 ± 4 days ($p = 2.5 \times 10^{-9}$). Evidence of clinical or histologic brain toxicity was minimal. In a second experiment, using drug-free polymer ($n = 7$), MST was 24 ± 3 days. This was compared against an MST of 24 ± 4 days in the tumor control group ($n = 7$) and 49 ± 7 days in a cisplatin-polymer treated group ($n = 6$). In a third experiment, two doses of drug-free polymer and three doses of cisplatin-loaded polymer were tested in normal nontumor-bearing rats and found to be well tolerated.

Conclusions: Intralesional sustained release of cisplatin from biodegradable polymer is safe and effective for the treatment of brain 9L gliosarcoma in rats. *J. Surg. Oncol. 64:268–273, 1997*

KEY WORDS: **brain neoplasm; 9L gliosarcoma; biodegradable polymer; sustained release; cisplatin**

INTRODUCTION: THE SEARCH FOR IMPROVED PROGNOSIS

The prognosis of patients with malignant glioma following conventional treatment (surgery, radiation, and systemic chemotherapy) is poor. Following treatment, 90% of lesions tend to recur within 2 cm of the primary site [1]. Local control of these tumors therefore becomes an important goal in prolonging patient survival. An encouraging strategy for local control has been the use of sustained drug release from biodegradable polymer. Preliminary work in this area for the treatment of brain tumors has been performed in animals [2–8] and on patients [9,10]. This latter trial was performed using the chemotherapeutic agent BCNU. Although BCNU has

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been the most effective chemotherapeutic agent for the treatment of brain tumors when given intravenously, cisplatin may be a better choice if administered intralesionally. Cisplatin does not readily cross the blood-brain barrier (BBB) [11,12], but it has a relatively high distribution within brain tumors [13]. These properties have the potential of minimizing systemic toxicity and decreasing the rate of elimination of the drug when administered within the brain locally [7]. In addition, the main target of cisplatin is cellular DNA [14–16], with those cells that are actively dividing being most vulnerable. Normal neurons, which are in a relatively dormant state, are preferentially spared.

Due to the above theoretical advantages, we tested the effect of intralesionally administered biodegradable polymer containing cisplatin for the treatment of intracranial gliosarcomas in rats. In our initial studies [17,18], the dose of cisplatin found to be most beneficial was 0.5 mg/m^2 as compared to 5 mg/m^2 and 25 mg/m^2. In this study, we report the safety and long-term (60 day) efficacy of intralesionally implanted cisplatin at a dose of 0.5 mg/m^2 in normal rats and in rats with 9L gliosarcoma.

MATERIALS AND METHODS

Five thousand 9L gliosarcoma tumor cells were injected (day 0) into the right frontal cortex of the Fischer 344 rat 7 days after a permanent cannula was installed into the right front lobe. The animal use protocol was reviewed and approved by the Institute of Animal Care and Use Committee (University of Colorado Health Sciences Center, Denver). This committee follows the Guide for the Care and Use of Laboratory Animals as established by the Institute of Laboratory Animal Resources Commission on Life Sciences of the National Research Council. The inoculated tumor cells were allowed to establish for 7 days prior to treatment. At this time, the tumor mass measured 0.2–0.4 cm in greatest diameter (data not shown). Open cell polylactic acid (OPLA® THM Biomedical, Duluth, MN) or cisplatin-loaded OPLA® equal to 0.5 mg/m^2 of cisplatin was then injected into the treatment groups. All survivors were sacrificed on day 60 in experiments one and two, and on day 40 in experiment three. Brains were then fixed in 10% formalin immediately following death or at the time of sacrifice.

Tumor Cells

A low passage number of 9L gliosarcoma cells, syngeneic to Fischer 344 rats, were cultured in Dulbecco's modified Eagle's medium containing 15% fetal calf serum (Gibco, Grand Island, NY), 200 mM L-glutamine, 100 U/ml penicillin, and 0.1 mg/ml streptomycin. Cells were cultured for 4–5 days, washed, and resuspended in phosphate-buffered saline before use.

Animals

Inbred pathogen-free male Fischer 344 rats weighing between 200–250 g were used (SASCO, Omaha, NE). All animals were required to undergo quarantine at our institution for 7 days prior to use.

Cannulation Procedure

Rats were anesthetized with the combination of intramuscularly administered Ketamine (44 mg/kg) and Rompun (8 mg/kg) and positioned in a stereotactic head frame. The head was shaved and prepped with iodine soap and alcohol. A coronal incision was then made with the underlying periosteum stripped free and the bone cleaned and dried. Three burr holes were placed in the left frontal and both parietal bones, respectively, with stainless steel screws (DIN 84A, 1 mm I.D. × 3 mm, AAA Metric Supply, Denver) secured into the holes. At a point 2 mm anterior and 3 mm lateral to the bregma, on the right side, a hole was drilled and the dura punctured. A 13 mm cannula (0.065″ O.D. × 0.053″ I.D., Small Parts, Miami, FL) anchored to a holding wire, was aligned vertically in the stereotactic frame and lowered 3 mm from the top of the cranium (4 mm down, then 1 mm up) into the right frontal lobe. Dental acrylic was placed around the anchoring screws and the cannula and allowed to set. The holding wire was then released from the stereotactic frame. A sterile stylet (0.050″ O.D.) was inserted into the cannula.

Infusion of Tumor Cells

Intracranial infusion of 9L gliosarcoma tumor cells was performed with unanesthetized rats wrapped in toweling with only their heads exposed. To infuse the cells, the stylet was removed from the cannula. Ten ml of phosphate-buffered saline (PBS) containing 5,000 9L tumor cells was drawn up into a flexible Teflon tubing (0.028″ O.D. × 0.022″ I.D., Small Parts) attached to a 50 μl Hamilton syringe. The cells were then infused into the brain over a 2 min period. When finished, the sterile stylet was re-inserted into the cannula.

Administration of Polymers

The open cell polylactic acid polymer (OPLA®) and polymer containing cisplatin (OPLA®-Pt) was provided by THM Biomedical. The polymer (OPLA®) was originally designed to act as an inert biodegradable scaffold for osteoconduction to repair defects of membranous bone. It more recently has been adapted as a vehicle for drug delivery. OPLA® is comprised of two differing groups of D, L-polylactic acid. Both polymer groups are

synthesized from the same monomer supply differing only in molecular weight; 50% of the polymer is high molecular weight (MW = 350,000) and 50% is low molecular weight (MW = 34,000). *Cis*-diamine-dichloroplatinum II (cisplatin) is joined to the low molecular weight fraction to create a cisplatin concentration of 8.2% by weight (OPLA®-Pt). Sterilization is achieved by exposure of the finished drug delivery vehicle to 2.5 Mrads of gamma irradiation. Detailed information about the internal architecture has been previously described [19]. Intracranial administration of OPLA® or OPLA®-Pt was performed in the unanesthetized rat. The rat was wrapped in toweling with only the head exposed. The stylet was removed from the previously placed cannula and preweighed doses of polymer were introduced into the cannula using a specifically designed plastic funnel. The polymer was then advanced intracranially through the cannula by use of a small plunger. When finished, the stylet was placed back into the cannula. OPLA® containing 0.5 mg/m^2 of cisplatin at 8.2% concentration (by weight) is 6.25 mg/m^2.

Histological Studies

All brains were fixed in 10% formalin for 1 week. Coronal sections, 5–6 μm thick, taken every 0.25 mm, were stained with hematoxylin and eosin. Specimens were examined by our neuropathologist (B.K.K.).

Statistics

Mean survival times were analyzed using the Student t-test and Log-Rank test. *P* values were considered significant if smaller than 0.05.

RESULTS

In experiment 1 (Fig. 1), mean survival in the 9L gliosarcoma containing rats treated with intralesional OPLA-Pt® was significantly improved (51 ± 14 days) over the tumor control group (24 ± 4 days) ($p = 2.5 \times 10^{-9}$). All 19 tumor control animals died between 19 and 33 days. In the treatment group, 3 of 19 rats died within 24 hours after polymer insertion and were excluded from the analysis. Of the remaining 16 animals, 10 survived to day 60 demonstrating no obvious neurophysiological deficits. The cause of death for all of the animals in the control group and 6 of 16 in the treatment group (those dying before day 60) was cerebral herniation secondary to increased intracranial pressure induced by a large intracranial tumor. The midline structures were shifted from right to left, away from the intracranial tumor. This is characteristic of animals in the 1 week established 9L gliosarcoma tumor model. In the treatment group, the rats that died prior to day 60 all demonstrated large intracranial tumors, which was the cause of death, with varying degrees of necrosis surrounding the polymer installation site. All 10 survivors in the treatment group

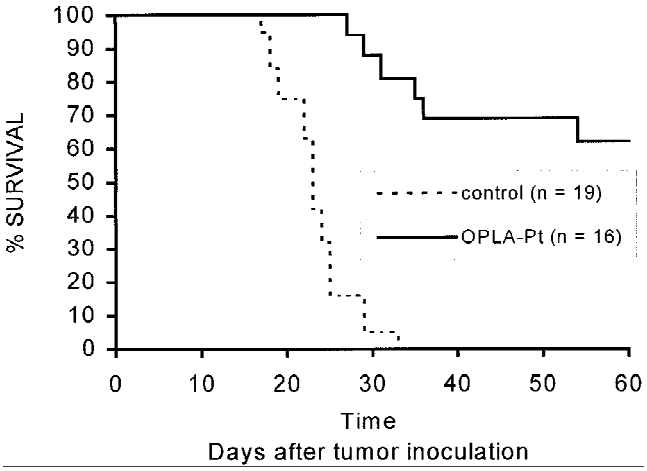

Fig. 1. Survival curve for 9L gliosarcoma tumor bearing rats with and without open cell polylactic acid polymer containing cisplatin (OPLA®-Pt) treatment. OPLA®-Pt (0.5 mg/m^2 of cisplatin) was administered intracranially 7 days after tumor injection. Long-term survivors were sacrificed on day 60. Mean survival in the treatment group (n = 16) was significantly prolonged ($P = 2.5 \times 10^{-9}$) as compared to tumor control (n = 19).

demonstrated no histologic evidence of tumor at sacrifice. Toxicity to the surrounding brain in all animals was minimal. Four of the 10 surviving animals did exhibit multilocated abscess cavities at the cannulation site. The wall of the cavities showed macrophages, chronic inflammatory cells, and fibroblasts. Neutrophilic debris was noted occasionally, with varying amounts of residual polymer also noted.

In experiment 2, cisplatin-loaded polymer (OPLA®-Pt) was compared with the drug-free polymer (OPLA®) for the treatment of rats with 1 week established intracranial 9L gliosarcoma. Mean survival of animals was 24 ± 4 days, 24 ± 3 days and 49 ± 17 days in the tumor control (n = 6), OPLA® treated (n = 7) and OPLA®-Pt treated (n = 6) groups, respectively. Long-term (60 days) survivors (4/6) were seen only in the OPLA®-Pt treated group (Fig. 2), with the histology demonstrating no viable tumors. Survival in group three was significantly improved over groups one and two ($P < 0.0001$). In group two, the tumors were virtually the same size as those in group one, with polymer seen embedded centrally within the tumor with little or no surrounding reaction noted.

In experiment 3, six nontumor bearing rats (3 in each group) were treated with OPLA® at 6.58 mg/m^2 and 65.8 mg/m^2, respectively. Another nine rats (3 in each group) were treated with three doses of OPLA®-Pt (equal to 0.5, 1.0, and 2.0 mg/m^2 of cisplatin). All animals survived the full 40 days, with no neurophysiologic deficits noted during the entire posttreatment period. Histologically, in the rats treated with drug-free polymer, no significant cerebral reaction was observed. In the cisplatin-polymer treated groups, however, the area of tissue reaction varied

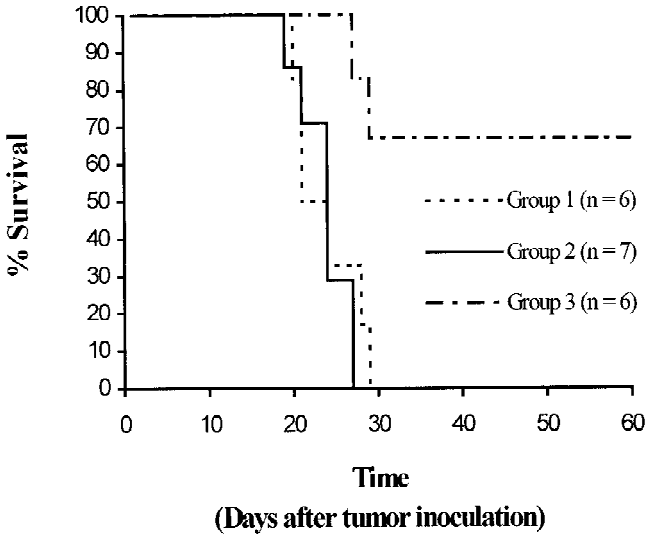

Fig. 2. Survival curve for 9L gliosarcoma tumor bearing rats without any treatment (group 1); treated with open cell polylactic acid polymer (OPLA®) (6.25 mg/m^2) (group 2) or 6.25 mg/m^2 of OPLA®-Pt (containing 0.5 mg/m^2 of cisplatin) (group 3). Long-term survivors were sacrificed on day 60. Mean survival in group 3 (n = 6) was significantly prolonged ($P < 0.0001$) as compared to tumor control (n = 6) and group 2 (n = 7).

with the dose of drug received. Even at the highest dose of OPLA-Pt (2 mg/m^2 cisplatin) the histologic reaction was mild and sharply demarcated from the normal appearing surrounding brain.

DISCUSSION

Delivery of chemotherapeutic agents to the brain for the treatment of intracranial neoplasms has been difficult. The main obstacle frustrating neuroscientists is the presence of the BBB [11,12]. Thompson et al. [11] demonstrated that when cisplatin is given intravenously, the cisplatin concentration in the sural nerve was 3.5 μg/g and 3.8 μg/g in spinal ganglia, but only 0.17 μg/g in the brain.

The presence of the BBB has resulted in many unique approaches being tried in order to increase the intracranial delivery of chemotherapeutic agents. One such attempt is to administer drug directly intracranially by intraarterial carotid or vertebral infusion. This, however, has been fraught with complications. Because the body surface area is highly variable compared to brain size [20], and there is significant maldistribution inside the infused arterial territory [21], intra-arterial (i.a.) chemotherapy has demonstrated unpredictable neurotoxicity [22] and only sporadic efficacy [21]. Regional toxicities to the eye, cochlea, and brain were found to be dose-limiting factors in this technique [21].

Temporary disruption of the BBB through the administration of intracarotid hyperosmolar mannitol followed by systemic or intracarotid chemotherapy is another approach to alter the BBB [23,24]. This approach allows drugs to be administered in conjunction with transient opening of the BBB to insure intracranial delivery. Osmotic disruption of the BBB, however, results in only a moderate increase in drug levels within the actual tumor and is offset by a relatively large increase in drug level in the surrounding normal brain [25]. This technique, therefore, carries the potential of increasing the exposure of the normal brain to the deleterious effects of the chemotherapeutic agents [26], with the tumor still exposed to a suboptimal drug level [27]. In an attempt to solve this problem, Black et al. [27] have tried to open the blood-tumor barrier (BTB) by intracarotid infusion of leukotriene C_4, which has been shown selectively to open the BTB by twofold, leaving the normal BBB intact. Theoretically, this technique seems promising but awaits further testing.

Techniques as outlined above are based on the premise of delivering a large amount of drug into a tumor over a short time interval. Normal cerebrospinal fluid flow dynamics are such that with bolus injection, rapid equilibration, and elimination of the drug is to be expected [28]. Any advantage gained in the preferential delivery of drug to the tumor is transient at best, being rapidly lost by drug diffusion along the very steep concentration gradient in surrounding brain tissue (sump or sink effect) [24]. Ideally, to be most effective, a drug should be in contact with the tumor at an effective concentration for a sufficient period of time while producing the least local and systemic toxicity. To meet this general therapeutic goal, the local sustained release of drug seems ideal. Use of biodegradable polymer is one such way to deliver the drug locally in a sustained release fashion.

BCNU, one of the most commonly used systemic drugs for the treatment of brain tumors, has been delivered by biodegradable polymer both in an animal model and clinically [4,5,9,10]. In the rat glioma model, the intracranial (i.c.) administration of BCNU in polymer to 4 day established intracranial 9L gliosarcoma was found to be superior to intraperitoneal (i.p.) BCNU administration at the same dose (14 mg/kg) [4]. Of note, however, in the nontumor-bearing animals treated with i.c. BCNU polymer and i.p. BCNU alone at the same dose, 8 of 12 and 10 of 12 animals, respectively, died during treatment, which questions the feasibility of this treatment. Further experiments testing the efficacy of paclitaxel [7] and 4-hydroperoxycyclophosphamide [8] delivered locally in polymer also have been recently reported. In a phase I/II clinical trial completed by Brem et al. [9], using BCNU impregnated biodegradable polymer (PPCA-SA) as a surgical adjunct to subtotally resected recurrent malignant gliomas, BCNU polymer was found to be well tolerated and safe. A phase III placebo-controlled efficacy trial has confirmed its efficacy, but the survival advantage was small [10]. In the past, the efficacy of a drug in

treating brain tumors has in large part been determined by its ability to permeate the BBB. For these reasons BCNU has been very attractive. With intralesional delivery, this becomes less important. A drug's ability to concentrate within the tumor [13] and not cross the BBB [11,12], as seen with cisplatin [13], may in fact be more desirable.

Local administration of cisplatin via polymers to non-central nervous system tumors has been investigated by several groups and found to be more effective and less toxic than systemic administration for the treatment of various soft tissue neoplasms [29–31]. Hecquet et al. [32], implanting a cisplatin containing lactic acid-glycolic acid copolymer into the renal parenchyma of mice, demonstrated the ability to obtain a continuous release of cisplatinum over 3 weeks. Straw et al. [19] found that cisplatin-impregnated polymer (OPLA-Pt®) was well tolerated in dogs treated locally for limb osteosarcoma. When OPLA-Pt® was implanted, very high local drug concentrations were obtained with decreased systemic drug concentration observed as compared to intravenous cisplatin administration. Krag et al. [33] performed intratumoral injections of cisplatin mixed with purified bovine collagen in humans with advanced superficial malignant melanoma. Of the tumors, 86% (12/14) regressed or stabilized, with 50% of the lesions regressing >50%. Theon et al. [34], using an intratumorally implanted controlled release formulation of cisplatin in sesame oil, found some degree of regression in a variety of tumors treated in horses. Complete response was observed in 18/19 sarcoid lesions, 5/7 squamous cell carcinomas, and 4/4 squamous cell papillomas.

Whereas the efficacy of locally implanted cisplatin in polymer has been reported for many extracranial tumors, experiments in its use in the treatment of intracranial tumors have not been performed. In 1982, Kroin and Penn [35] demonstrated intracerebral sustained microinfusion of 0.9 mg/hr of cisplatin by osmotic minipump for periods of up to 7 days in normal rat brains was well tolerated. They demonstrated that the concentration of cisplatin maintained in the brain parenchma for 1 cm surrounding the infusion site was sufficient to kill various tumor cell lines in vitro. They concluded that this could be a useful adjunct in the treatment of human brain neoplasms, but pursued this no further.

In this study, we evaluated the long-term efficacy and toxicity of sustained release cisplatin impregnated in biodegradable polymer in the treatment of brain tumors. The 9L gliosarcoma tumor model was used, which in our laboratory has been very reliable and reproducible [17,18,36,37]. In our previous work using the 9L gliosarcoma model in rats, three doses of OPLA-Pt (0.5 mg/m^2, 5 mg/m^2, and 25 mg/m^2 of cisplatin) were tested and all demonstrated complete tumor eradication at day 30 [17,18]. Neurotoxicity, however, was significant at the 5 mg/m^2 and 25 mg/m^2 doses. At the 0.5 mg/m^2 dose, which is <1% of the recommended systemic dosage for the treatment of brain tumors, neurotoxicity was minimal. In this report, polymer containing <2 mg/m^2 of cisplatin was found to be well tolerated. No systemic toxic reaction, reflected by a change in average body weight or general neurophysiological behavior, was seen. Long-term survivors, 10/16 in experiment one and 4/6 in experiment two, were seen only in the cisplatin-treated group, with the mean survival significantly prolonged as compared to tumor control animals and drug-free, polymer-treated animals. At autopsy no evidence of viable tumor was noted in the survivors. In the OPLA-Pt-treated animals that did succumb to progressive tumor, varying degrees of tumor necrosis were found around the residual polymer. This feature was absent in the tumor control animals. Our studies further demonstrated that drug-free polymer alone was inert when placed intracranially in normal rats and also demonstrated no inherent tumoricidal ability in tumor bearing animals. The abscess cavities noted at the site of the cannula in some of the long-term survivors is not surprising in light of the fact that the permanently implanted cannulae had been in place for 67 days. Abscess cavities were not noted in our previous experiments when survivors were sacrificed on day 30 [17,18] and day 40 (data not shown), respectively.

CONCLUSIONS

Intralesionally administered cisplatin loaded in biodegradable polymer for the treatment of intracranial 9L gliosarcoma in rats is safe and effective. Based on the theoretical advantages mentioned above and the results reported in this study, we are encouraged by the results of locally administered cisplatin impregnated biodegradable polymer for the treatment of intracranial tumors. Further studies testing the in vitro and in vivo release of cisplatin from polymer as well as the optimum dosage schedule for tumors with a given size are underway.

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